the humanized heavy chain comprises complementarity determining regions that are identical to the corresponding complementarity determining regions of the mouse 21-4 heavy chain, except that the CDR3 region of the humanized heavy chain may or may not comprise a phenylalanine residue at position H98.

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25. The method according to claim 24, wherein the amino acid sequence of the mature light chain variable region is the sequence designated La (SEQ ID NO:7) in Fig. 6 and the amino acid sequence of the mature heavy chain variable region is Ha (SEQ ID NO:11) in Fig. 7.

26. The method according to claim 25, wherein the humanized antibody is a Fab fragment.

REMARKS

STATUS OF THE CLAIMS

After entrance of the amendment, claims 1-26 are pending. The claims were amended to conform to U.S. Patent and Trademark Office practice. As suggested by the examiner, "use" claims are prosecuted as "methods of use" claims. Therefore, the claims were amended accordingly and discussed further below. Claim amendments are for purposes of improved clarity or consistency of claim language unless otherwise noted.

Applicants use the paragraph numbering in the Office Communication (Paper Number 11) in responding to the examiner's remarks. Claims 1-26 are pending in the present application.

1. The examiner stated that for examination purposes, "use" claims are prosecuted as "methods of use" claims. The examiner further reminded Applicants that "use" claims are subject to rejections under 35 U.S.C. §§101 and 112, second paragraph. For this reason, the examiner requested the claims be amended accordingly. Applicants' representative has amended the claims as suggested by the examiner.

2. Applicants' representative appreciates the examiner's comments regarding reviewing the specification and to amend the specification with SEQ. ID NOs: , if appropriate. Applicants' representative notes that the communication filed on April , 2001 has placed the instant application in compliance with the Sequence Rules. Applicants' representative agrees to review and amend the specification by the time the application is in condition for allowance and make the appropriate amendments, if necessary.

3. The specification has been amended to insert an updated reference to the priority applications. No new matter has been introduced.

4. Regarding the examiner's comment that no Information Disclosure Statement (IDS) has been filed with the instant application, Applicants' representative filed an IDS and Form PTOL-1449 on October 9, 2001 together with 34 references.

5. The examiner stated that the instant application contains claims directed to the following patentably distinct species of the claimed invention: wherein the disease is selected from:

(A) asthma;

(B) atherosclerosis;

(C) AIDS dementia;

(D) diabetes;

(E) IBD;

(F) arthritis;

(G) transplant rejection;

(H) GVHD;

(I) tumor metastasis;

(L) psoriasis;

(M) ischemia;

(N) acute leukocyte-mediated lung injury; or

(O) ARDS.

The examiner stated that these species are distinct because the pathological conditions differ in etiologies and therapeutic endpoints. The examiner further stated that Applicants must elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable.

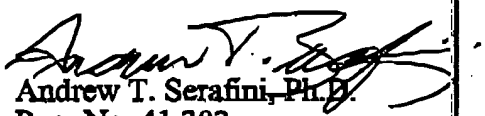
Applicants hereby elect to prosecute the species (F), rheumatoid arthritis, without traverse.

CONCLUSION

Applicants request that the application now be examined on the merits.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (650) 326-2400.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

--CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of USSN 08/561,521, filed November 21, 1995, which issued as U.S. Patent No. 5,840,299 on November 24, 1998, which is incorporated by reference in their entirety for all purposes.--

IN THE CLAIMS:

Please amend claims 1-26 as follows (Applicants have attached the claims with markings to show changes made as an appendix):

1. (AMENDED) [Use of]A method of using a humanized antibody to alpha-4 integrin in the manufacture of a medicament for treating a disease selected from the group consisting of asthma, atherosclerosis, AIDS dementia, diabetes, inflammatory bowel disease, rheumatoid arthritis, transplant rejection, graft versus host disease, tumor metastasis, nephritis, atopic dermatitis, psoriasis, myocardial ischemia, and acute leukocyte mediated lung injury.

2. (AMENDED) The [use]method according to claim 1, wherein the disease is asthma.

3. (AMENDED) The [use]method according to claim 1, wherein the disease is atherosclerosis.

4. (AMENDED) The [use]method according to claim 1, wherein the disease is AIDS dementia.

5. (AMENDED) The [use]method according to claim 1, wherein the disease is diabetes.

6. (AMENDED) The [use]method according to claim 1, wherein the disease is inflammatory bowel disease.

7. (AMENDED) The [use]method according to claim 1, wherein the disease is rheumatoid arthritis.

8. (AMENDED) The [use]method according to claim 1, wherein the disease is transplant rejection.

9. (AMENDED) The [use]method according to claim 1, wherein the disease is graft versus host disease.

10. (AMENDED) The [use]method according to claim 1, wherein the disease is tumor metastasis.

11. (AMENDED) The [use]method according to claim 1, wherein the disease is nephritis.

12. (AMENDED) The [use]method according to claim 1, wherein the disease is atopic dermatitis.

13. (AMENDED) The [use]method according to claim 1, wherein the disease is psoriasis.

14. (AMENDED) The [use]method according to claim 1, wherein the disease is myocardial ischemia.

15. (AMENDED) The [use]method according to claim 1, wherein the disease is acute leukocyte-mediated lung injury.

16. (AMENDED) The [use]method according to claim 1[7], wherein the disease is adult respiratory distress syndrome.

17. (TWICE AMENDED) The [use]method according to claim 1, wherein the humanized antibody is a humanized form of the mouse 21.6 antibody.

18. (AMENDED) The [use]method according to claim 17, wherein the humanized antibody comprises a humanized heavy chain and a humanized light chain:

(1) the humanized light chain comprising three complementarity determining regions (CDR1, CDR2 and CDR3) having amino acid sequences from the corresponding complementarity determining regions of the mouse 21-6 immunoglobulin light chain variable domain designated SEQ[.] ID[.] No[.]: 2, and a variable region framework from a human kappa light chain variable region framework sequence except

in at least one position selected from a first group consisting of L45, L49, L58 and L69, wherein the amino acid position is occupied by the same amino acid present in the equivalent position of the mouse 21-6 immunoglobulin light chain variable region framework; and

(2) the humanized heavy chain comprising three complementarity determining regions (CDR1, CDR2 and CDR3) having amino acid sequences from the corresponding complementarity determining regions of the mouse 21-6 immunoglobulin heavy chain variable domain designated SEQ[.] ID[.] No[.]: 4, and a variable region framework from a human heavy chain variable region framework sequence except in at least one position selected from a second group consisting of H27, H28, H29, H30, H44, H71, wherein the amino acid position is occupied by the same amino acid present in the equivalent position of the mouse 21-6 immunoglobulin heavy chain variable region framework;

wherein the humanized immunoglobulin specifically binds to alpha-4 integrin with a binding affinity having a lower limit of about 10^7 M^{-1} and an upper limit of about five-times the binding affinity of the mouse 21-6 immunoglobulin.

19. (AMENDED) The [use]method according to claim 18, wherein the humanized light chain variable region framework is from an RE1 variable region framework sequence except in at least one position selected from the first group, and except in at least one position selected from a third group consisting of positions L104, L105 and L107, wherein the amino acid position is occupied by the same amino acid present in the equivalent position of a kappa light chain from a human immunoglobulin other than RE1.

20. (AMENDED) The [use]method according to claim 19, wherein the humanized heavy chain variable region framework is from a 21/28'CL variable region framework sequence.

21. (AMENDED) The [use]method according to claim 20, wherein the humanized light chain variable region framework comprises at least three amino acids from the mouse 21.6 immunoglobulin at positions in the first group and three amino acids

from the kappa light chain from the human immunoglobulin other than REI at positions in the third group, and the humanized heavy chain variable region framework comprises at least five amino acids from the mouse 21.6 immunoglobulin at positions in the second group.

22. (AMENDED) The [use]method according to claim 21, wherein the humanized light chain variable region framework is identical to the RE1 light chain variable region framework sequence except for the at least three positions from the first group and the three positions from the third group, and the heavy chain variable region framework is identical to the 21/28'CL heavy chain variable region framework sequence except for the at least five positions from the second group.

23. (AMENDED) The [use]method according to claim 22, wherein [the] at least three positions from the first group are positions L45, L58 and L69, and the at least five positions from the second group are positions H27, H28, H29, H30 and H71.

24. (AMENDED) The [use]method according to claim 23, wherein the humanized light chain comprises complementarity determining regions that are identical to the corresponding complementarity determining regions of the mouse 21-6 heavy chain, and the humanized heavy chain comprises complementarity determining regions that are identical to the corresponding complementarity determining regions of the mouse 21-6 heavy chain, except that the CDR3 region of the humanized heavy chain may or may not comprise a phenylalanine residue at position H98.

25. (AMENDED) The [use]method according to claim 24, wherein the amino acid sequence of the mature light chain variable region is the sequence designated La (SEQ[.] ID NO:7) in Fig. 6 and the amino acid sequence of the mature heavy chain variable region is Ha (SEQ[.] ID NO:11) in Fig. 7.

26. (AMENDED) The [use]method according to claim 25, wherein the humanized antibody is a Fab fragment.